REMARKS

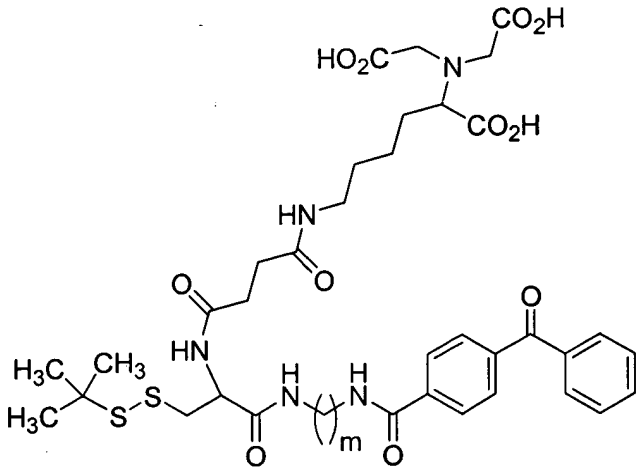
A. Status of the Claims

Claims 2-4, 6-8, 11, 13-23, 25, 28, 30, and 32-77 are canceled without prejudice to future prosecution. Claims 1, 24, 26, 29 and 31 are amended, and claim 78 is added. Therefore, claims 1, 5, 9-10, 12, 24, 26-27, 29, 31, and 78 are pending after entry of this amendment.

B. Support for the Amendments

Claims 1, 24, 26, 29, and 31 have been amended to more clearly recite the nature of the functional groups X, Y, and Z and/or the covalent core. Claim 78 has been added. Support for the amendments and new claim 78 can be found throughout the specification and claims as originally filed.

Claims 1, 24, 26, 29, and 31 now encompass heterofunctional reagents containing a glycine amino acid as the covalent core. Support for a heterofunctional reagent having a glycine core is found in the specification, for example, on page 65, Example 2, compound x:



x

Additional support for heterofunctional reagents with a glycine core is found in the specification on page 23, line 12, to page 24, line 5.

Claims 1, 24, 26, 29, and 31 now recite that X is a non-covalent protein tag binder "that specifically binds to a protein tag portion of a protein." Support for this phrase can be found in the specification, for example, on page 13, lines 1-14, which states, in part:

> Protein tag binders preferably bind their binding partners in a substantially specific manner. Protein tag binders having a dissociation constant (K_D) of less than about 10^{-6} M are preferred. Antibodies or antibody fragments are highly suitable as protein tag binders. Antigens may also serve as protein tag binders as they are capable of binding antibodies. A receptor which binds a protein ligand is another example of a possible protein tag binder. Protein tag binders as used herein are understood to be limited to agents which only interact with their binding partners through non-covalent, reversibly covalent, or weakly covalent interactions.

The "binding partner" to which the protein tag binder associates may be a protein tag, as recited on page 13, lines 15-17: "The term 'protein tag' or 'binding partner' means that portion of a protein which is bound by a particular protein tag binder, preferably in a substantially specific manner." Additional support for this phrase may be found on page 25, line 27, to page 30, line 26.

Claims 1, 24 and 31 now recite that Y is a photoactivatable covalent crosslinking group "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag." Claim 26 now recites that Y' is "the residue of a photoactivatable covalent crosslinking group after formation of a covalent linkage to said protein, said photoactivatable covalent crosslinking group covalently attached at or adjacent to said protein tag." Claim 29 now recites that Y' is "a photocrosslinking group that has been activated and covalently attached to a protein at or adjacent to said protein tag." Support for these phrases can be found in the specification, for example, on page 2, lines 18-20, which states:

> X is a specific protein tag binder which binds a protein at a specific region or regions within the protein...Y is an activatable, preferably photoactivatable, covalent crosslinking group adapted to link the heterofunctional crosslinker covalently at or adjacent the specific region or regions of the protein....

The "specific region or regions" to which the protein tag binder associates may be a protein tag, as recited on page 13, lines 15-17: "The term 'protein tag' or 'binding partner' means that portion

of a protein which is bound by a particular protein tag binder, preferably in a substantially specific manner." Additional support for these phrases may be found on page 20, line 31 to page 21, line 2, which states:

> [T]he site for covalent attachment of functional group Y will depend on the lengths and flexibility of the linking groups L^1 and L^2. Typically, the site for covalent attachment of Y to the protein will be between the site of binding of X and about one diameter of the protein, preferably about 50 Å, more preferably about 25 Å, and still more preferably about or less than 10 Å.

Claims 1 and 26 now recite that Z is a "protected or unprotected chemical crosslinking group that covalently links the heterofunctional crosslinking reagent to a label or support wherein Z is rendered inactive when protected." Support for this phrase can be found in the specification, for example, on page 31, line 31, to page 32, line 1:

> Functional group Z is a reactive group which can form a covalent link to another molecule, label or support, and which is optionally protected. Preferably, Z is a group which can participate in a chemoselective ligation reaction having little or no cross reactivity with functional groups present in the amino acids that make up the protein being modified.

Additional support is found on page 32, line 20, to page 33, line 2, which states in part:

> Z will in some embodiments be protected, or otherwise rendered inactive to covalent bond formation, by a protecting group. A variety of protecting groups are useful in the invention and can be selected based on the functionality present in Z. The term "protecting group" as used herein, refers to any of the groups which are designed to block one reactive site in a molecule while a chemical reaction is carried out at another reactive site.

New claim 78 recites that X is "an antibody or antibody fragment." Support for this phrase may be found, for example, in the specification on page 29, lines 3-7:

> In another group of embodiments, the protein tag binder is a group which binds an endogenous protein tag (e.g., an epitope on the protein). In this group of embodiments, the protein tag binder will typically be an antibody or antibody fragment which is sufficient to form a non-covalent association complex with the protein tag or epitope.

In light of the above remarks, Applicants respectfully submit that no new matter is introduced with this amendment.

C. Rejection of Claims for Containing Allegedly Improper Markush Group

Claims 1, 2, 4, 5, 9, 10, 12, 13, 24, 26, 27, 29, 31, and 34 stand rejected as allegedly being drawn to an improper Markush group. The Examiner asserts that the core component, W, includes essentially all trivalent moieties which do not contain common structural features. The Examiner further asserts that amino acids, the suggested subgenus for W, do not share a substantial structural feature disclosed as being essential to the disclosed utility.

Applicants respectfully disagree with the Examiner's assertion that amino acids do not share a substantial structural feature. However, to expedite prosecution, Applicants have amended claims 1, 24, 26, 29, and 31 to encompass only those heterofunctional reagents containing a glycine covalent core. Applicants reserve the right to prosecute claims in future divisional applications drawn to heterofunctional crosslinking reagents containing additional covalent core chemical moieties.

In light of the amendments to claims 1, 24, 26, 29, and 31, Applicants respectfully request withdrawal of the rejection.

D. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4, 5, 9, 10, 12, 24, 26, 27, 29, 31, and 34 stand rejected under 35 U.S.C. §112, first paragraph as indefinite. The Examiner asserts that the subject matter encompassed by the terms "W," "X," "Y," and "Z" are unclear. More specifically, the Examiner asserts that the conditions for activating the crosslinking group "Y" are unclear, the purpose of protecting "Z" is unclear, and that the structural and functional features of "W" are unclear. Applicants respectfully submit that the subject matter encompassed by the terms "W," "X," "Y," and "Z" are clear in claims 1, 24, 26, 29, and 31 as amended.

Claims 1, 24, 26, 29, and 31 now encompass only those heterofunctional reagents containing a glycine as the covalent core. Therefore, Applicants respectfully submit that claims

1, 24, 26, 29, and 31, as amended, clearly define the structural and functional features of the covalent core.

Claims 1, 24, 26, 29, and 31 now recite that X is a non-covalent protein tag binder "that specifically binds to a protein tag portion of a protein." As amended, the claims encompass protein tag binders that *specifically* and *non-covalently* bind to a protein tag portion of a protein. Applicants respectfully submit that, with the addition of this phrase, the claims clearly define the subject matter encompassed by the protein tag binder X.

Claims 1, 24 and 31 now recite that Y is a photoactivatable covalent crosslinking group "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag." Claim 26 now recites that Y' is "the residue of a photoactivatable covalent crosslinking group after formation of a covalent linkage to said protein, said photoactivatable covalent crosslinking group covalently attached at or adjacent to said protein tag." Claim 29 now recites that Y' is "a photocrosslinking group that has been activated and covalently attached to a protein at or adjacent to said protein tag." Because the claims 1, 24 and 31 as amended recite that Y is a *photo*activatable crosslinking group, claim 26 as amended recites that Y' is the residue of a *photo*activatable covalent crosslinking group, and claim 29 as amended recites that Y' is a *photo*crosslinking group, the claims clearly define the crosslinking conditions. In addition, the claims as amended now specify that the photocrosslinking occurrs "at or adjacent to" the protein tag portion of the protein. The specification explains that the distance, if any, between the protein tag and the site of attachment of Y or Y' is typically no more than about one diameter of the protein:

> [T]he site for covalent attachment of functional group Y will depend on the lengths and flexibility of the linking groups L^1 and L^2. Typically, the site for covalent attachment of Y to the protein will be between the site of binding of X and about one diameter of the protein, preferably about 50 Å, more preferably about 25 Å, and still more preferably about or less than 10 Å. *See* page 20, line 31 to page 21, line 2.

Therefore, Applicants respectfully submit that, with the addition of this phrase, the claims clearly define the subject matter encompassed by the terms Y and Y'.

Claims 1 and 26 now recite that Z is "a protected or unprotected chemical crosslinking group that covalently links the heterofunctional crosslinking reagent to a label or support wherein Z is rendered inactive when protected." The claims as amended recite that Z is inactive when protected, thus preventing covalent bond formation while a chemical reaction is carried out at another reactive site. *See* page 32, lines 20, to page 33, line 2, quoted above. Therefore, Applicants respectfully submit that, with the addition of this phrase, the claims clearly recite the purpose of protecting Z.

Because the claims as amended clearly define the subject matter encompassed by the terms "W", "X," "Y," and "Z," Applicants respectfully request the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

E. Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4, 5, 9, 10, 12, 24, 26, 27, 29, 31, and 34 stand rejected under 35 U.S.C. §112, first paragraph as failing enable one skilled in the art to practice the entire scope of the claimed invention. The Examiner suggests amending the claims to recite that Y is adapted to link the heterofunctional crosslinking reagent at or adjacent to specific regions of the protein and Z attaches the heterofunctional crosslinking reagent to a label or solid support.

In response to the Examiner's suggestions, Applicants have amended claims 1, 24, 26, 29, and 31. Claims 1, 24 and 31 now specify that Y is a photoactivatable covalent crosslinking group "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag." Claim 26 now specifies that Y' is "the residue of a photoactivatable covalent crosslinking group after formation of a covalent linkage to said protein, said photoactivatable covalent crosslinking group covalently attached at or adjacent to said protein tag." Claim 29 now specifies that Y' is "a photocrosslinking group that has been activated and covalently attached to a protein at or adjacent to said protein tag."

In addition, claims 1 and 26 now recite that Z is "a protected or unprotected chemical crosslinking group that covalently links the heterofunctional crosslinking reagent to a label or support wherein Z is rendered inactive when protected."

In light of these amendment, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

F. Rejections under 35 U.S.C §102(b)

Claims 1 and 2 stand rejected as allegedly anticipated by Roberts *et al.*, *Basic Principles of Organic Chemistry*, (hereinafter referred to as "Roberts"), claims 1, 2, 4, 9, 12, 24, 26, 29, and 31 stand rejected as allegedly anticipated by Inman *et al.*, U.S. Patent No. 5,444,150 (hereinafter referred to as "Inman"), and claims 1, 2, 4, 9, 12, 24, 26, 29, and 31 stand rejected as allegedly anticipated by Oh *et al.*, U.S. Patent No. 5,851,778 (hereinafter referred to as "Oh").

The Federal Circuit has held that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See MPEP § 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Applicants respectfully submit that the claims as amended are not anticipated by any of the references of record because none of the cited references disclose every element of the amended claims.

1. Roberts *et al.*, *Basic Principles of Organic Chemistry*

The Examiner asserts that trifunctional amino acids (such as cysteine, threonine, serine, and aspartic acid) disclosed in Roberts anticipate claims 1 and 2.

Applicants respectfully submit that the trifunctional amino acids do not anticipate claims 1 and 2 as amended. Claim 1 now recites that X is a non-covalent protein tag binder "that specifically binds to a protein tag portion of a protein," and that Y is a photoactivatable covalent crosslinking group "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag." None of the trifunctional amino acids disclosed in Roberts contain a protein tag binder or a photoactivatable crosslinker as recited in amended claim 1.

The heterofunctional crosslinker of amended claim 1 contains X, which is a *non-covalent* protein tag binder "that *specifically* binds to a protein tag portion of a protein." The Roberts amino acids do not disclose protein tag binders that *specifically* and *non-covalently* bind to a protein.

To specifically bind the protein tag portion, the specification teaches that the protein tag binder must "preferably bind" the protein tag portion over other portions of the protein. *See* page 13, lines 1-14. The trifunctional amino acids disclosed in Roberts do not contain a functional group capable of preferably binding a protein tag portion. Rather, the functional groups of the Roberts trifunctional amino acids are only capable of forming *non-specific* covalent linkages to the protein. For example, a thiol functional group will nonspecifically bind to any available cysteine side chain on a given protein; a carboxylic acid functional group will nonspecifically bind to any available amino group on the protein; and an amino functional group will nonspecifically bind to any available carboxyl group on the protein. Therefore, none of the functional groups of Roberts read on the protein tag binder X as claimed in amended claim 1.

The heterofunctional crosslinker of amended claim 1 also contains the photoactivatable covalent crosslinking group Y, which is "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag." A photoactivatable crosslinking group is reactive in response to "a particular portion of the electromagnetic spectrum," and are preferably "reactive in response to ultraviolet or visible portions of the light spectrum." *See* page 30, lines 27-34. None of the Roberts trifunctional amino acids contain a functional group that is reactive in response to a portion of the electromagnetic spectrum. Therefore, none of the functional groups of Roberts read on the photoactivatable covalent crosslinking group Y as claimed in amended claim 1.

Because the trifunctional amino acids of Roberts to not contain all of the elements of amended claim 1, Applicants respectfully request withdrawal of the rejection.

2. Inman *et al.*, U.S. Patent No. 5,444,150

The Examiner asserts that the trifunctional compounds of Inman anticipate the compounds of claim 1, wherein X is Br, and Y and Z are COOH or CH_3-$C(CH_3)_2$-O-C(O)-NH-. Applicants respectfully submit that the trifunctional compounds of Inman do not anticipate claims 1, 24, 26, 29, and 31 as amended.

Claim 1, 24, 26, 29, and 31 now recite that X is a *non-covalent* protein tag binder "that *specifically* binds a protein tag portion of a protein." In addition, claims 1, 24 and 31 now recite that Y is a photoactivatable covalent crosslinking group "adapted to covalently link the heterofunctional crosslinking reagent at or adjacent to said protein tag;" claim 26 recites that Y' is "the residue of a photoactivatable covalent crosslinking group;" and claim 29 recites that Y' is a "photocrosslinking group that has been activated and covalently attached."

As explained above, Applicants' teach that to specifically bind the protein tag portion, the protein tag binder must "preferably bind" the protein tag portion over other portions of the protein. *See* page 13, lines 1-14. Inman discloses trifunctional compounds containing "a haloacetyl or other haloacyl functional group." *See* column 4, lines 30-31. However, the haloacetyl or haloacyl functional groups do not preferably bind a protein tag portion. Rather, the haloacetyl or haloacyl functional groups form *non-specific* linkages to any and all available thiols on a given protein, such as the side chain of cysteine residues. Moreover, the haloacetyl or haloacyl functional groups *covalently* bind to a protein. Therefore, the haloacetyl or haloacyl functional groups do not read on the protein tag binder X, as recited in amended claims 1, 24, 26, 29, and 31.

As also explained above, a photoactivatable crosslinking group is reactive in response to "a particular portion of the electromagnetic spectrum," and are preferably "reactive in response to ultraviolet or visible portions of the light spectrum." *See* page 30, lines 27-34. The Inman COOH and CH_3-$C(CH_3)_2$-O-C(O)-NH- functional groups are not reactive in response to electromagnetic radiation. Therefore, the functional groups COOH and CH_3-$C(CH_3)_2$-O-C(O)-NH- do not read on the photoactivatable covalent crosslinking group Y in amended claims 1, 24 and 31, the residue of a photoactivatable covalent crosslinking group Y' in amended claim 26, and the photocrosslinking group Y' in amended claim 29.

3. Oh *et al.*, U.S. Patent No. 5,851,778

The Examiner asserts that the compounds of Oh as disclosed in figures 7 and 9, anticipate the compounds of claim 1. Applicants respectfully submit that the trifunctional conjugates of Oh do not anticipate claims 1, 24, 26, 29, and 31 as amended.

Claims 1, 24, 26, 29, and 31, as amended, are drawn to a heterofunctional crosslinking reagent having a glycine covalent core. The *non-covalent* protein tag binder X is attached to the amino group of the glycine core through linker L^1. The photoactivatable covalent crosslinking group Y is attached to the carboxyl group of the glycine core through linker L^2. The group Z is attached to the glycine core central carbon through linker L^3.

The trifunctional conjugate disclosed in figure 9 of Oh contains a boronic acid "guiding member" that forms a covalent bond with a polysaccharide group on a protein. *See* column 19, lines 54-55. This boronic acid group does not read on the protein tag binder X for two reasons. First, amended claims 1, 24, 26, 29, and 31 require that the protein tag binder X form a *non-covalent bond* with the protein tag. The boronic acid group is disclosed as forming *covalent* bonds with a polysaccharide group on a protein.

Second, the protein tag binder X is attached to the *amino* group of the glycine core via linker L^1 whereas the boronic acid group is attached to the *carboxyl* group of the central core via an amine linker. Rather than a protein tag binder attached to the *amino* functionality of the trifunctional conjugate, the compound of figure 9 contains a nitrophenylazido group attached to the *amino* functionality. The nitrophenylazido group does not read on the protein tag binder X because it is a *non-specific* photoactivatable crosslinker and, thus, not "capable of specifically binding a protein tag portion of a protein."

In addition, the trifunctional conjugate disclosed in figure 9 of Oh contains a biotin moiety attached via a heteroalkyl linker to the core central carbon. The biotin moiety is an "intended label." *See* column 19, line 57. Although the biotin intended label is attached to the core central carbon, it does not read on group Z of the amended claims because it is not capable of *covalently linking* the heterofunctional crosslinking reagent to a label or support. Rather, the biotin moiety is only capable of *non-covalently* binding a ligand containing a binding partner such as streptavidin. Therefore, the biotin intended label is not a group "that covalently links the heterofunctional crosslinking reagent to a label or support" as recited in claims 1 and 26.

With regard to figure 7 of Oh, the Examiner apparently asserts that the nitrophenylazido group of figure 7 corresponds to groups Y or Y'. However, Applicants respectfully assert that the trifunctional conjugate disclosed in figure 7 of Oh does not anticipate

the heterofunctional reagents of claims 1, 24, 26, 29, and 31. First, the photoactivatable nitrophenylazido group of figure 7 is not attached to the central core through the core carboxyl group, as required in claims 1, 24, 26, 29, and 31. Second, if it is asserted that the nitrophenylazido group of figure 7 corresponds to groups Y or Y' of the amended claims, then the compound of figure 7 does not contain a group Z that covalently links the heterofunctional crosslinking reagent to a label or support. Therefore, the compound of figure 7 does not read on the heterofunctional compounds of amended claims 1, 24, 26, 29, and 31.

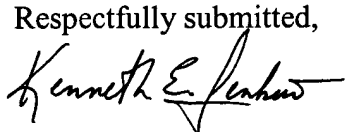
Because none of the cited references anticipate all the elements of claims 1, 24, 26, 29, and 31, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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